

2025 RELEASE UNDER E.O. 14176

<120> METHOD OF DETERMINING EVOLUTIONARY POTENTIAL OF MUTANT
RESISTANCE GENES AND USE THEREOF TO SCREEN FOR DRUG
EFFICACY

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<150> 60/149,813

<151> 1999-08-19

<160> 17

<170> PatentIn Ver. 2.1

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<213> Artificial Sequence

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 taagatcact accgggcgta ttttttagt tatcgagatt ttcaggagct aaggaagcta 4980
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aacattttga ggcatttcag tcagttgctc aatgtaccta taaccagacc gttcagctgg 5100
 atattacggc ctttttaaag accgtaaaga aaaataagca caagttttat cgggccttta 5160
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<210> 4
 <211> 1134
 <212> DNA
 <213> Unknown Organism

<220>
 <223> Description of Unknown Organism: Escherichia coli
 plasmid pBR322

<400> 4
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 atccccgggta tggcgggtggc ggtaatttat cagggtaaac cttattactt tacctggggc 180
 tatgcggaaca tcgccaaaaa gcagcccgtc acacagcaaa cgttgtttga gttaggttcg 240
 gtcagcaaaa catttactgg cgtgcttggt ggcgacgcta ttgctcgagg ggaaatcaag 300
 ttaagcgatc ccacaacaaa atactggcct gaacttaccg ctaaacagtg gaatgggatc 360
 acactattac atctcgcaac ctacactgct ggccggcctgc cattgcagggt gccggatgag 420
 gtgaaatcct caagcgactt gctgcgcttc tatcaaaact ggcagcctgc atggggtcca 480
 ggaacacaac gtctgtatgc caactccagt atcggtttgt tcggcgccact ggctgtgaag 540
 cegtctggtt tgagttttga gcaggcgatg caaactcgtg tcttccagcc actcaaactc 600
 aaccatacgt ggattaatgt accgcccgcga gaagaaaaga attacgcctg gggatatcgc 660
 gaaggtaagg cagtgcattg ttgcgctggg gcgttagatg ctgaagctta tgggtgtgaag 720
 tcgaccattg aagatatggc ccgctgggtg caaagcaatt taaaaccctt tgatatcaat 780
 gagaaaacgc ttcaacaagg gatacaactg gcacaatctc gctactggca aaccggcgat 840
 atgtatcagg gcctgggctg ggaaatgctg gactggcccg taaatcctga cagcatcatt 900
 aacggcagtg acaataaaat tgcactggca gcacgccccg taaaagcgat tacgccccca 960
 actcctgcag tacgcgcata atgggtacat aaaacagggg cgaccggcgg atttggttagc 1020
 tatgtcgcgt ttattccaga aaaagagctg ggtatcgtga tgctggcaaa caaaaactat 1080
 cccaatccag cgagagtcga cgccgcctgg cagattctta acgctctaca gtaa 1134

<210> 5
 <211> 377
 <212> PRT
 <213> Unknown Organism

<220>
 <223> Description of Unknown Organism: Escherichia coli
 plasmid pBR322

<400> 5
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 1 5 10 15

Thr Phe Ala Ala Pro Gln Gln Ile Asn Asp Ile Val His Arg Thr Ile
 20 25 30

Thr Pro Leu Ile Glu Gln Gln Lys Ile Pro Gly Met Ala Val Ala Val
 35 40 45

Ile Tyr Gln Gly Lys Pro Tyr Tyr Phe Thr Trp Gly Tyr Ala Asp Ile
 50 55 60

Ala Lys Lys Gln Pro Val Thr Gln Gln Thr Leu Phe Glu Leu Gly Ser
 65 70 75 80

Val Ser Lys Thr Phe Thr Gly Val Leu Gly Gly Asp Ala Ile Ala Arg
 85 90 95

Gly Glu Ile Lys Leu Ser Asp Pro Thr Thr Lys Tyr Trp Pro Glu Leu
 100 105 110

Thr Ala Lys Gln Trp Asn Gly Ile Thr Leu Leu His Leu Ala Thr Tyr
 115 120 125

Thr Ala Gly Gly Leu Pro Leu Gln Val Pro Asp Glu Val Lys Ser Ser
 130 135 140

Ser Asp Leu Leu Arg Phe Tyr Gln Asn Trp Gln Pro Ala Trp Ala Pro
 145 150 155 160

Gly Thr Gln Arg Leu Tyr Ala Asn Ser Ser Ile Gly Leu Phe Gly Ala
 165 170 175

Leu Ala Val Lys Pro Ser Gly Leu Ser Phe Glu Gln Ala Met Gln Thr
 180 185 190

Arg Val Phe Gln Pro Leu Lys Leu Asn His Thr Trp Ile Asn Val Pro
 195 200 205

Pro Ala Glu Glu Lys Asn Tyr Ala Trp Gly Tyr Arg Glu Gly Lys Ala
 210 215 220

Val His Val Ser Pro Gly Ala Leu Asp Ala Glu Ala Tyr Gly Val Lys
 225 230 235 240

Ser Thr Ile Glu Asp Met Ala Arg Trp Val Gln Ser Asn Leu Lys Pro
 245 250 255

Leu Asp Ile Asn Glu Lys Thr Leu Gln Gln Gly Ile Gln Leu Ala Gln
 260 265 270

09640382 081800

Ser Arg Tyr Trp Gln Thr Gly Asp Met Tyr Gln Gly Leu Gly Trp Glu
275 280 285

Met Leu Asp Trp Pro Val Asn Pro Asp Ser Ile Ile Asn Gly Ser Asp
290 295 300

Asn Lys Ile Ala Leu Ala Ala Arg Pro Val Lys Ala Ile Thr Pro Pro
305 310 315 320

Thr Pro Ala Val Arg Ala Ser Trp Val His Lys Thr Gly Ala Thr Gly
325 330 335

Gly Phe Gly Ser Tyr Val Ala Phe Ile Pro Glu Lys Glu Leu Gly Ile
340 345 350

Val Met Leu Ala Asn Lys Asn Tyr Pro Asn Pro Ala Arg Val Asp Ala
355 360 365

Ala Trp Gln Ile Leu Asn Ala Leu Gln
370 375

<210> 6

<211> 1134

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: mutant
ampicillin resistance gene AmpC13A

<400> 6

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atcccgggta tggcggtggc ggtaatttat cagggtaaac cttattactt tacctggggc 180
tatgcggaca tcgctaaaaa gcagcccgtc acacagcaaa cgttgtttga gttagggttcg 240
gtcagcaaaa catttactgg cgtgcttggg ggcgacgcta ttgctcgagg ggaaatcaag 300
ttaagcgatc ccacaacaaa atactggcct gaacttaccg ctaaacagtg gaatgggatc 360
acactattac atctcgcaac ctacactgct ggcggcctgc cattgcaggt gccggatgag 420
gtgaaatcct caagcgactt gctgcgcttc tatcaaaact ggcagcctgc atgggctcca 480
ggaacacaac gtctgtatgc caactccagt atcggtttgt tcggcgcaact ggctgtgaag 540
ccgtctgggt tgagttttga gcaggcgatg caaactcgtg tyttccagcc actcaaactc 600
aaccatacgt ggattaatgt accgcccga gaagaaaaga attacgcctg gggatatcgc 660
gaaggtaagg cagtgcattg ttcgcctggg gcgtagatg ctgaagctta tgggtgtgaag 720
tcgaccattg aagatatggc ccgctgggtg caaagcaatt taaaaccctt tgatatcaat 780
gagaaaacgc ttcaacaagg gatacaactg gcacaatctc gctactggca aaccggcgat 840
atgtatcagg gcctgggctg ggaaatgctg gactggccgg taaatcctga cagcatcatt 900

aacggccgtg acaataaaat tgcactggca gcacgccccg taaaagcgat tacgccccca 960
 actcctgcag tacgcgcata atgggtacat aaaacagggg cgaccggcgg atttggttagc 1020
 tatgtcgcgt ttattccaga aaaagagctg ggtatcgtga tgctggcaaa caaaaactat 1080
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<210> 7

<211> 377

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: mutant
 ampicillin resistance protein AmpC13A

<400> 7

Met Val Lys Thr Thr Leu Cys Ala Leu Leu Ile Thr Ala Ser Cys Ser
 1 5 10 15

Thr Phe Ala Ala Pro Gln Gln Ile Asn Asp Ile Val His Arg Thr Ile
 20 25 30

Thr Pro Leu Ile Glu Gln Gln Lys Ile Pro Gly Met Ala Val Ala Val
 35 40 45

Ile Tyr Gln Gly Lys Pro Tyr Tyr Phe Thr Trp Gly Tyr Ala Asp Ile
 50 55 60

Ala Lys Lys Gln Pro Val Thr Gln Gln Thr Leu Phe Glu Leu Gly Ser
 65 70 75 80

Val Ser Lys Thr Phe Thr Gly Val Leu Gly Gly Asp Ala Ile Ala Arg
 85 90 95

Gly Glu Ile Lys Leu Ser Asp Pro Thr Thr Lys Tyr Trp Pro Glu Leu
 100 105 110

Thr Ala Lys Gln Trp Asn Gly Ile Thr Leu Leu His Leu Ala Thr Tyr
 115 120 125

Thr Ala Gly Gly Leu Pro Leu Gln Val Pro Asp Glu Val Lys Ser Ser
 130 135 140

Ser Asp Leu Leu Arg Phe Tyr Gln Asn Trp Gln Pro Ala Trp Ala Pro
 145 150 155 160

Gly Thr Gln Arg Leu Tyr Ala Asn Ser Ser Ile Gly Leu Phe Gly Ala
 165 170 175

Leu Ala Val Lys Pro Ser Gly Leu Ser Phe Glu Gln Ala Met Gln Thr
 180 185 190

Arg Val Phe Gln Pro Leu Lys Leu Asn His Thr Trp Ile Asn Val Pro
 195 200 205

Pro Ala Glu Glu Lys Asn Tyr Ala Trp Gly Tyr Arg Glu Gly Lys Ala
 210 215 220

Val His Val Ser Pro Gly Ala Leu Asp Ala Glu Ala Tyr Gly Val Lys
 225 230 235 240

Ser Thr Ile Glu Asp Met Ala Arg Trp Val Gln Ser Asn Leu Lys Pro
 245 250 255

Leu Asp Ile Asn Glu Lys Thr Leu Gln Gln Gly Ile Gln Leu Ala Gln
 260 265 270

Ser Arg Tyr Trp Gln Thr Gly Asp Met Tyr Gln Gly Leu Gly Trp Glu
 275 280 285

Met Leu Asp Trp Pro Val Asn Pro Asp Ser Ile Ile Asn Gly Arg Asp
 290 295 300

Asn Lys Ile Ala Leu Ala Ala Arg Pro Val Lys Ala Ile Thr Pro Pro
 305 310 315 320

Thr Pro Ala Val Arg Ala Ser Trp Val His Lys Thr Gly Ala Thr Gly
 325 330 335

Gly Phe Gly Ser Tyr Val Ala Phe Ile Pro Glu Lys Glu Leu Gly Ile
 340 345 350

Val Met Leu Ala Asn Lys Asn Tyr Pro Asn Pro Ala Arg Val Asp Ala
 355 360 365

Ala Trp Gln Ile Leu Asn Ala Leu Gln
 370 375

<210> 8

<211> 1134

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: mutant

ampicillin resistance gene AmpC41A

<400> 8

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atccccgggta tggcgggtggc ggtaatttat cagggtaaac cttattactt tacctggggc 180
tatgcgggaca tcgctaaaaa gcagcccgtc acacagcaaa cgttggttga gttagggttcg 240
gtcagcaaaa catttactgg cgtgcttggt ggcgacgcta ttgctcgagg ggaaatcaag 300
ttaagcgatc ccacaacaaa atactggcct gaacttacgg ctaaacagtg gaatgggatc 360
tcactattac atctcgcaac ctacactgct ggcggcctgc cattgcaggt gccggatgag 420
gtgaaatcct caagcgactt gctgcgcttc tatcaaaact ggcagcctgc atgggctcca 480
ggaacacaac gtctgtatgc caactccagt atcggtttgt tcggcgccact ggctgtgaag 540
ccgtctgggt tgagttttga gcaggcgatg caaactcgtg tcttccagcc actcaaactc 600
aaccatacgt ggattaatgt accgcccgcga gaagaaaaga attacgcctg gggatatcgc 660
gagggtaagg cagtgcattg ttgcctggg gcgtagatg ctgaagctta tgggtgtgaag 720
tcgaccattg aagatatggc ccgctgggtg caaagcaatt taaaaccctc tgatatcaat 780
gagaaaacgc ttcaacaagg gatacaactg gcacaatctc gctactggca aaccggcgat 840
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tatgtcgcgt ttattccaga aaaagagctg ggtatcgtga tgctggcaaa caaaaactat 1080
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<210> 9

<211> 377

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: mutant
ampicillin resistance protein AmpC41A

<400> 9

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Met Val Lys Thr Thr Leu Cys Ala Leu Leu Ile Thr Ala Ser Cys Ser
1           5           10           15

```

```

Thr Phe Ala Ala Pro Gln Gln Ile Asn Asp Ile Val His Arg Thr Ile
20           25           30

```

```

Thr Pro Leu Ile Glu Gln Gln Lys Ile Pro Gly Met Ala Val Ala Val
35           40           45

```

```

Ile Tyr Gln Gly Lys Pro Tyr Tyr Phe Thr Trp Gly Tyr Ala Asp Ile
50           55           60

```

```

Ala Lys Lys Gln Pro Val Thr Gln Gln Thr Leu Phe Glu Leu Gly Ser
65           70           75           80

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[illegible]

Ala Trp Gln Ile Leu Asn Ala Leu Gln
370 375

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<210> 10
<211> 1134
<212> DNA
<213> Artificial Sequence
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<220>
<223> Description of Artificial Sequence: mutant
ampicillin resistance gene AmpC21B

<400> 10						
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cctcaacaaa	tcaacgatat	tgtgcatcgc	acaattacc	cgcttataga	gcaacaaaag	120
atcccgggta	tggcggtggc	ggtaatttat	cagggtaaac	cttattactt	tacctggggc	180
tatgcggaca	tcgccaaaaa	gcagcccgtc	acacagcaaa	cgttgtttga	gttaggttcg	240
gtcagcaaaa	catttactgg	cgtgcttggt	ggcgacgcta	ttgctcgagg	ggaaatcaag	300
ttaagcgatc	ccacaacaaa	atactggcct	gaacttaccg	ctaaacagtg	gaatgggatc	360
acactattac	atctcgcaac	ctacactgct	ggcggcctgc	cattgcaggt	gccggatgag	420
gtgaaatcct	caagcgactt	gctgcgcttc	tatcaaaact	ggcagcctgc	atgggctcca	480
ggaacacaa	gtctgtatgc	caactccagt	atcggtttgt	tcggcgcact	ggctgtgaag	540
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aaccatacgt	ggattaatgt	accgcccgc	gaagaaaaga	attacgcctg	gggatatcgc	660
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tcgaccattg	aagatatggc	ccgctgggtg	caaagcaatt	taaaacccct	tgatatcaat	780
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atgtatcagg	gcctgggctg	ggaaatgcgg	gactggccgg	taagtcttga	cagcatcatt	900
aacggcagtg	acaataaaat	tgcactggca	gcacgccccg	taaaagcgat	tacgccccca	960
actcctgcag	tacgcgcatt	atgggtacat	aaaacagggg	cgaccggcgg	atttggttagc	1020
tatgtcgcgt	ttattccaga	aaaagagctg	ggtatcgtga	tgctggcaaa	caaaaactat	1080
cccaatccag	cgagagtcga	cgccgcctgg	cagattctta	acgctctaca	gtaa	1134

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<210> 11
<211> 377
<212> PRT
<213> Artificial Sequence
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<220>

Ser Thr Ile Glu Asp Met Ala Arg Trp Val Gln Ser Asn Leu Lys Pro
 245 250 255

Leu Asp Ile Asn Glu Lys Thr Leu Gln Gln Gly Ile Gln Leu Ala Gln
 260 265 270

Ser Arg Tyr Trp Gln Thr Gly Asp Met Tyr Gln Gly Leu Gly Trp Glu
 275 280 285

Met Arg Asp Trp Pro Val Ser Pro Asp Ser Ile Ile Asn Gly Ser Asp
 290 295 300

Asn Lys Ile Ala Leu Ala Ala Arg Pro Val Lys Ala Ile Thr Pro Pro
 305 310 315 320

Thr Pro Ala Val Arg Ala Ser Trp Val His Lys Thr Gly Ala Thr Gly
 325 330 335

Gly Phe Gly Ser Tyr Val Ala Phe Ile Pro Glu Lys Glu Leu Gly Ile
 340 345 350

Val Met Leu Ala Asn Lys Asn Tyr Pro Asn Pro Ala Arg Val Asp Ala
 355 360 365

Ala Trp Gln Ile Leu Asn Ala Leu Gln
 370 375

<210> 12

<211> 35

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: primer

<400> 12

gggggggtggc catcatgttt gacagcttat catcg

35

<210> 13

<211> 23

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: primer

<400> 13
caggctgaaa atcttctctc atc

23

<210> 14
<211> 25
<212> DNA
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: primer

<400> 14
tcacccggct cgtataatgt gtgga

25

<210> 15
<211> 20
<212> DNA
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: primer

<400> 15
atcgcggtccg ccatctccag

20

<210> 16
<211> 25
<212> DNA
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: primer

<400> 16
aaaaccatgg tcaaaacgac gctct

25

<210> 17
<211> 25
<212> DNA
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: primer

<400> 17

gttgggtcct ggccactagt acttc

25

09640832-081800